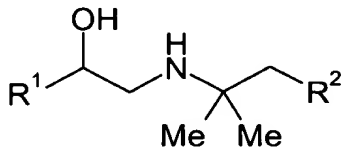
BETAMIMETICS HAVING A LONG-LASTING ACTIVITY, PROCESSES FOR PREPARING THEM, AND THEIR USE AS MEDICAMENTS

The present invention relates to new betamimetics of formula **1**



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wherein the groups R^1 and R^2 have the meanings given in the claims and specification, processes for preparing them, and their use as medicaments.

Background to the Invention

Betamimetics (β-adrenergic substances) are known from the prior art. They may be used in a variety of therapeutic applications.

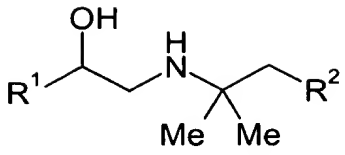
For drug treatment of diseases, it is often desirable to prepare medicaments with a longer duration of activity. As a rule, this ensures that the concentration of the active substance in the body needed to achieve the therapeutic effect is present over a longer period of time without the need to administer the drug repeatedly and frequently. The administration of an active substance at longer intervals of time also contributes considerably to the patient's well-being.

The aim of the present invention is to prepare betamimetics which are characterized by a longer duration of activity and can thus be used to prepare pharmaceutical compositions which have a longer-lasting activity.

Detailed Description of the Invention

Surprisingly, it has been found that the aim specified above is solved by compounds of formula **1**.

Accordingly the present invention relates to compounds of formula **1**



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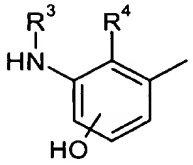
wherein:

R^1 is a group



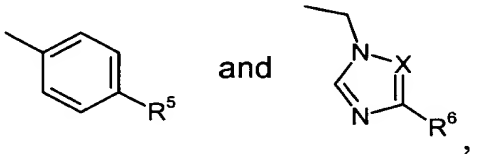
wherein

R^3 is benzyl group optionally substituted by a methoxy group,

R^4 is a hydrogen atom, or

R^3 and R^4 together are a -CO-CH_2-O- bridge, the carbonyl group of this bridge being bound to the nitrogen; and

R^2 is a group selected from



wherein

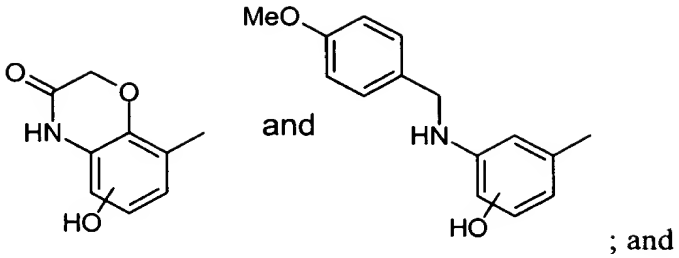
R^5 is a dimethylamino, methoxy, or butoxy group,

X is a nitrogen or a carbon atom, and

R^6 is a methoxyphenyl group, if X is nitrogen, or is an anellated phenyl ring, which is also linked to X, if X is carbon.

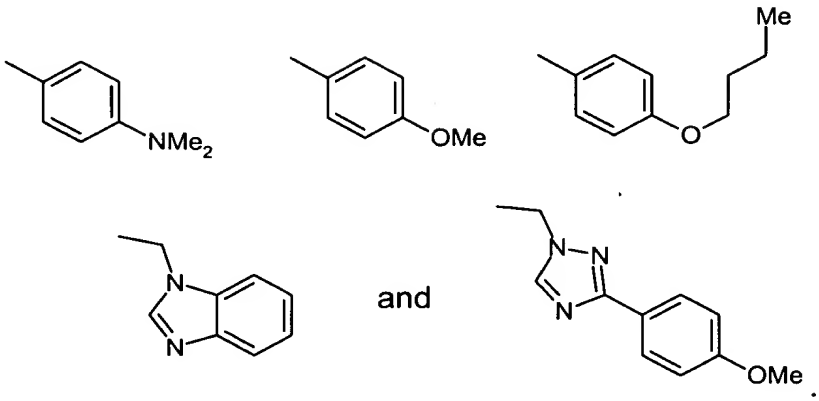
Preferred compounds of formula **1** are those wherein

R^1 is a group selected from



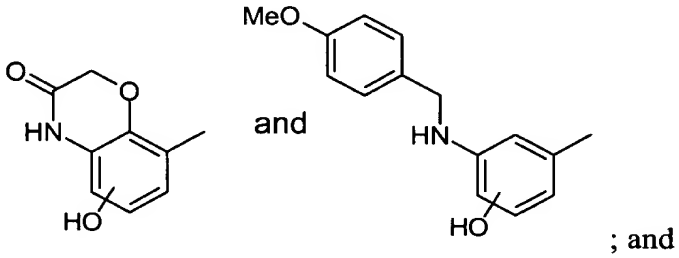
; and

R^2 is a group selected from



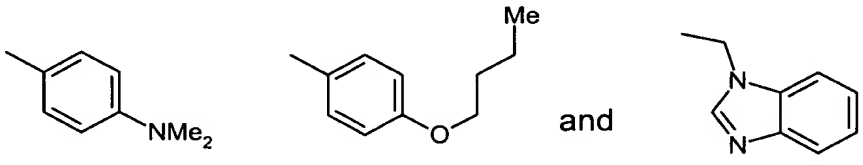
Particularly preferred are compounds of formula **1**, wherein:

R^1 is a group selected from



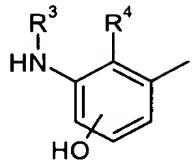
; and

R^2 is a group selected from



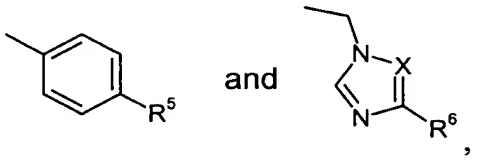
Of particular importance according to the invention are compounds of formula **1**, wherein

R^1 is a group



wherein R^3 and R^4 together are a -CO-CH_2-O- bridge, the carbonyl group of this bridge being bound to the nitrogen; and

R^2 is a group selected from



wherein

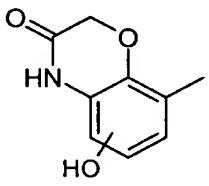
R^5 is a dimethylamino, methoxy, or butoxy group,

X is a nitrogen or a carbon atom, and

R^6 is a methoxyphenyl group, if X is nitrogen or an anellated phenyl ring which is also linked to X, if X is carbon.

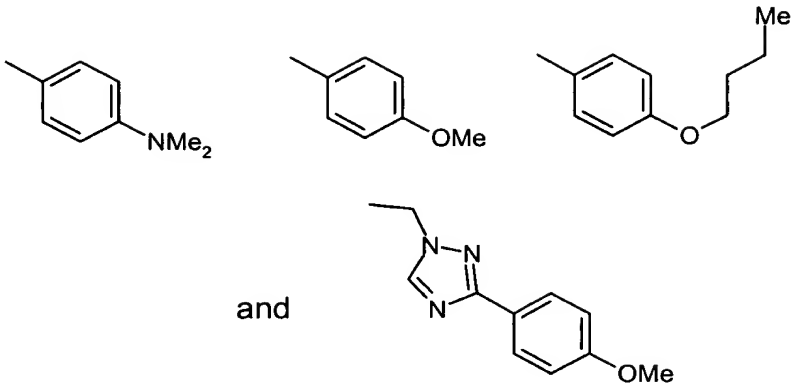
Preferred compounds of formula **1** are those wherein

R^1 is

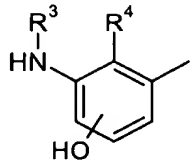


; and

R^2 is a group selected from



Of equivalent importance according to the invention are compounds of formula **1**, wherein R^1 is a group



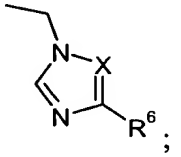
,

wherein

R^3 is a benzyl group optionally substituted by a methoxy group, and

R^4 is a hydrogen atom; and

R^2 is a group



;

wherein

X is a nitrogen or a carbon atom, and

R^6 is a methoxyphenyl group, if X is nitrogen, or an anellated phenyl ring which is also linked to X, if X is carbon.

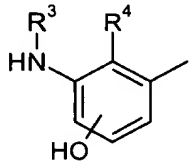
Of outstanding importance according to the invention are the following compounds of formula **1**:

a. 1-[3-(4-methoxybenzylamino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol;

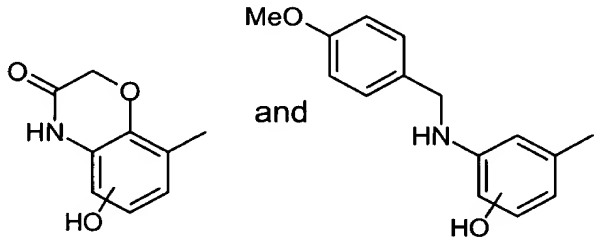
b. 1-[2*H*-5-hydroxy-3-oxo-4*H*-1,4-benzoxazin-8-yl]-2-[3-(4-*N*,*N*-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol; and

c. 1-[2*H*-5-hydroxy-3-oxo-4*H*-1,4-benzoxazin-8-yl]-2-[3-(4-*n*-butyloxyphenyl)-2-methyl-2-propylamino]ethanol.

In the compounds of formula **1** according to the invention, R^1 may be the group



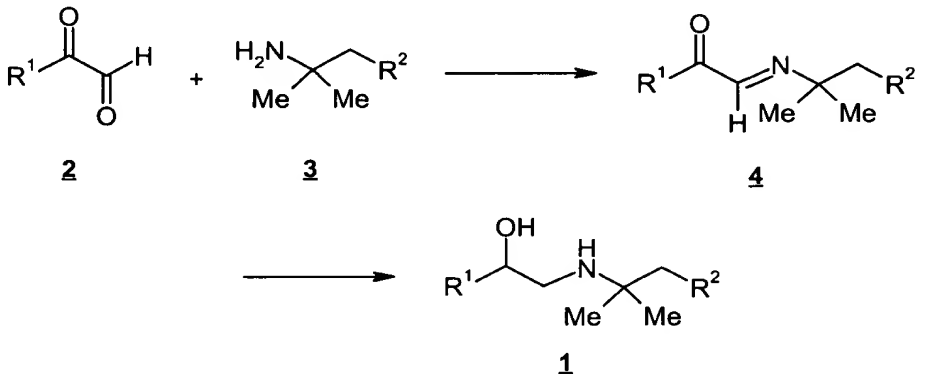
and preferably one of the groups



Of the compounds of formula **1** according to the invention, the ones which are particularly preferred are those wherein the hydroxyl group in the abovementioned groups R^1 is in the *ortho* or *meta* position relative to the amino substituent. Most preferably, the hydroxy group is in the *ortho* position to the amino group.

The invention relates to the compounds of formula **1** optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates as well as in the form of the free bases or the corresponding acid addition salts thereof with pharmacologically acceptable acids, such as, for example, acid addition salts with hydrohalic acids (e.g., hydrochloric or hydrobromic acid) or organic acids such as acetic, oxalic, fumaric, diglycolic, or methanesulfonic acid. Of the acid addition salts mentioned above, the salts of hydrochloric, methanesulfonic, and acetic acid are particularly preferred according to the invention.

The compounds according to the invention may be prepared, as described below, partly analogously to procedures which are already known in the prior art (Scheme 1 below).



2 3 4 1

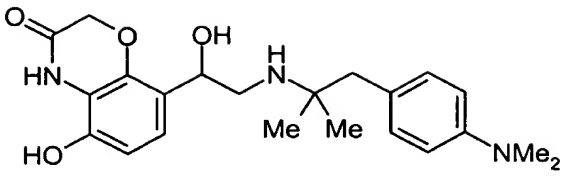
SCHEME 1

Scheme 1

Starting from suitably substituted aldehydes **2**, which may optionally be present in the form of their hydrates, the reaction is carried out with the amines **3** to form the Schiff's bases of formula **4**. Methods of forming Schiff's bases are known from the prior art. These Schiff's bases are finally reduced to form the compounds of formula **1** according to the invention. This reduction may be carried out, for example, with metal salt hydrides of the sodium borohydride type analogously to known standard methods. It may possibly be necessary to use protecting groups (e.g., a benzyl protecting group); their use and subsequent removal are known to those skilled in the art.

The Examples of synthesis described below serve to illustrate the present invention further. They must only be taken as examples of procedure, to illustrate the invention further, without restricting the invention to the object described below by way of example.

Example 1: 1-[2*H*-5-hydroxy-3-oxo-4*H*-1,4-benzoxazin-8-yl]-2-[3-(4-*N*,*N*-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol:



Preparation of the Schiff's base (compound of formula 4)

19.1 g (0.058 mol) of [2*H*-5-benzyloxy-3-oxo-4*H*-1,4-benzoxazin-8-yl]glyoxal hydrate is added to a solution of 250 mL of ethanol and 9.6 g (0.05 mol) of 3-(4-*N*,*N*-dimethylaminophenyl)-2-methyl-2-propylamine heated to 70°C and stirred for 15 minutes. After cooling, the crystals precipitated are suction filtered and dried.

Yield: 24 g (99% of theory); melting point: 201°C-204°C.

Reduction of the Schiff's base to obtain 1-[2*H*-5-benzyloxy-3-oxo-4*H*-1,4-benzoxazin-8-yl]-2-[3-(4-*N*,*N*-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol:

24 g of the Schiff's base (0.0495 mol) obtained is suspended in a mixture of 120 mL of ethanol/120 mL of dioxane and combined with 2 g of $NaBH_4$ within 30 minutes at 10°C-20°C and stirred for one hour. After the addition of 10 mL of acetone, the mixture is stirred for 30 minutes, diluted with 300 mL of ethyl acetate, the ethyl acetate phase is washed twice with about 200 mL of water, dried with sodium sulfate, and the solvent is distilled off *in vacuo*. The dihydrochloride is isolated from the residue with alcohol/acetone by acidifying with concentrated hydrochloric acid and suction filtering.

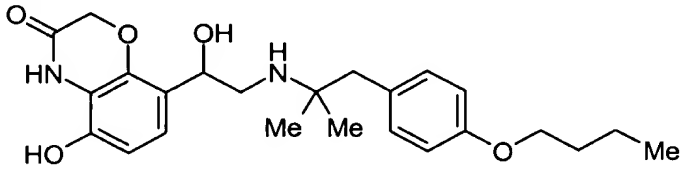
Yield: 17.5 g (62.6 % of theory); melting point: 180°C-185°C.

Cleaving of the protecting group to obtain the title compound:

3.5 g of the benzyl compound obtained above (0.0066 mol) is hydrogenated in 75 mL of methanol with the addition of 0.5 g of Pd/C at ambient temperature and normal pressure. The catalyst is suction filtered, the filtrate is evaporated down, screened, and the crystals precipitated are separated off.

Yield: 2.4 g (82.8% of theory); melting point: 216°C-218°C (hydrochloride).

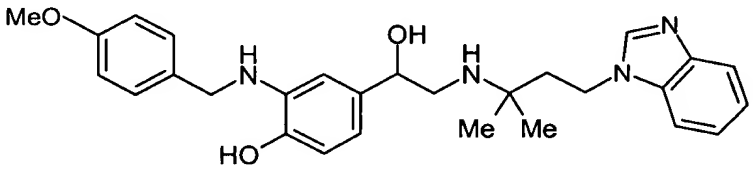
Example 2: 1-[2*H*-5-hydroxy-3-oxo-4*H*-1,4-benzoxazin-8-yl]-2-[3-(4-*n*-butyloxyphenyl)-2-methyl-2-propylamino]ethanol:



The title compound is prepared analogously to the method in Example 1.

Melting point: 189°C-190°C (methanesulfonate).

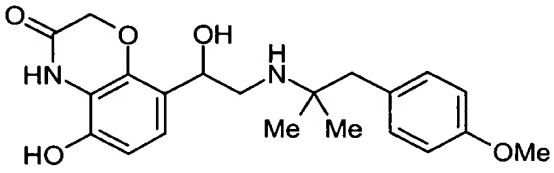
Example 3: 1-[3-(4-methoxybenzylamino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol:



The title compound is prepared analogously to the method in Example 1.

Melting point: 154°C-155°C (acetate).

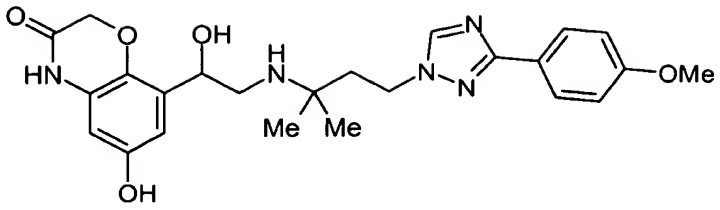
Example 4: 1-[2*H*-5-hydroxy-3-oxo-4*H*-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol:



The title compound is prepared analogously to the method in Example 1.

Melting point: 202°C-205°C (hydrochloride).

Example 5: 1-[2*H*-5-hydroxy-3-oxo-4*H*-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol:



The title compound is prepared analogously to the method in Example 1.
Melting point: 175°C-179°C (hydrochloride).

As has been found, the compounds of formula **1** are characterized by their range of uses in the therapeutic field. Particular mention should be made of those applications for which the compounds of formula **1** according to the invention may preferably be used on the basis of their pharmaceutical activity as betamimetics. These include, for example, the treatment of bronchial asthma (relaxation of the bronchial muscle), the treatment of the inflammatory component in COPD, the inhibition of premature labor in midwifery (tocolysis), the restoration of the sinus rhythm in the heart in cases of atrio-ventricular block as well as the correcting of bradycardiac heart rhythm disorders (antiarrhythmic agent), the treatment of circulatory shock (vasodilatation and increasing the heart-time volume) as well as the treatment of itching and skin inflammation.

The compounds of formula **1** may be used on their own or in conjunction with other active substances of formula **1** according to the invention. If desired, the compounds of formula **1** may also be used in conjunction with other pharmacologically active substances. These may be, in particular, anticholinergics, possibly other betamimetics, antiallergics, PAF antagonists, leukotriene antagonists, and steroids, as well as combinations of active substances.

Examples of anticholinergics which may be mentioned include ipratropium bromide, oxitropium bromide, and particularly tiotropium bromide. Drug combinations which contain tiotropium bromide as an additional active substance as well as the compounds of formula **1** according to the invention are particularly preferred according to the invention.

This combination is particularly important in the treatment of asthma or COPD, particularly COPD.

Suitable preparations for administering the compounds of formula **1** include, for example, tablets, capsules, suppositories, solutions, etc. The content of the pharmaceutically active compound(s) should be in the range from 0.05 to 90 wt.%, preferably 0.1 to 50 wt.%, of the composition as a whole. Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example, inert diluents such as calcium carbonate, calcium phosphate, or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example, collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities, the core may also consist of a number of layers. Similarly, the tablet coating may consist of a number or layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol, or sugar and a flavor enhancer, e.g., a flavoring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as *p*-hydroxybenzoates.

Solutions are prepared in the usual way, e.g., with the addition of isotonic agents, preservatives such as *p*-hydroxybenzoates, or stabilizers such as alkali metal salts of ethylenediamine tetraacetic acid (EDTA), optionally using emulsifiers and/or dispersants, whereas if water is used as the diluent, for example, organic solvents may optionally be

used as solvating agents or dissolving aids, and transferred into injection vials or ampoules or infusion bottles.

Capsules containing one or more active substances or combinations of active substances may, for example, be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules. Suitable suppositories may be made, for example, by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof. Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (e.g., petroleum fractions), vegetable oils (e.g., groundnut or sesame oil), mono- or polyfunctional alcohols (e.g., ethanol or glycerol), carriers such as natural mineral powders (e.g., kaolins, clays, talc, chalk), synthetic mineral powders (e.g., highly dispersed silicic acid and silicates), sugars (e.g., cane sugar, lactose, and glucose), emulsifiers (e.g., lignin, spent sulfite liquors, methylcellulose, starch, and polyvinylpyrrolidone) and lubricants (e.g., magnesium stearate, talc, stearic acid, and sodium lauryl sulfate).

The preparations are administered by the usual methods, preferably by inhalation in the treatment of asthma or COPD. For oral administration, the tablets may, of course, contain, apart from the abovementioned carriers, additives such as sodium citrate, calcium carbonate, and dicalcium phosphate together with various additives such as starch, preferably potato starch, gelatine, and the like. Moreover, lubricants such as magnesium stearate, sodium lauryl sulfate, and talc may be used at the same time for the tabletting process. In the case of aqueous suspensions, the active substances may be combined with various flavor enhancers or colorings in addition to the excipients mentioned above.

The dosage of the compounds according to the invention is naturally highly dependent on the method of administration and the complaint which is being treated. When administered by inhalation, the compounds of formula **1** are characterized by a high potency even at doses in the µg range. The compounds of formula **1** may also be used effectively above the µg range. The dosage may then be in the gram range, for example.

The examples of formulations which follow illustrate the present invention without restricting its scope:

Examples of pharmaceutical formulations

A. Tablets	per tablet
active substance	100 mg
lactose	140 mg
corn starch	240 mg
polyvinylpyrrolidone	15 mg
magnesium stearate	5 mg
	500 mg

The finely ground active substance, lactose, and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated, and dried. The granules, the remaining corn starch, and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

B. Tablets	per tablet
active substance	80 mg
lactose	55 mg
corn starch	190 mg
microcrystalline cellulose	35 mg
polyvinylpyrrolidone	15 mg
sodium-carboxymethyl starch	23 mg
magnesium stearate	2 mg
	400 mg

The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened.

The sodium carboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

C. Ampoule solution

active substance	50 mg
sodium chloride	50 mg
water for inj.	5 mL

The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilized and sealed by fusion. The ampoules contain 5 mg, 25 mg, and 50 mg of active substance.

D. Metering aerosol

active substance	0.005
sorbitan trioleate	0.1
monofluorotrichloromethane and difluorodichloromethane (2:3)	ad 100

The suspension is transferred into a conventional aerosol container with a metering valve. Preferably, 50 µl of suspension are delivered per spray. The active substance can also be in a higher dose if desired (e.g., 0.02 wt.%).

E. Solutions (in mg/100 mL)

active substance	333.3 mg
tiotropium bromide	333.3 mg
benzalkonium chloride	10.0 mg
EDTA	50.0 mg
HCl (1N)	ad pH 3.4

This solution can be produced in the usual way.

F. Inhalable powder

active substance	6 µg
tiotropium bromide	6 µg
lactose monohydrate	ad 25 mg

The inhalable powder is prepared in the usual way by mixing the individual ingredients together.